

## **CLAIMS**

1. compound of formula I, or a pharmaceutically acceptable salt or ester thereof

In which

R is H, -R2, -OR2 or NR1R2,

wherein R1 is H, lower alkyl or C3 to C10 cycloalkyl, and

R2 is lower alkyl or C<sub>3</sub> to C<sub>10</sub> cycloalkyl, and

wherein R1 and R2 are independently, optionally substituted by halo, hydroxy, lower alkoxy, CN, NO<sub>2</sub>, or optionally mono- or di-lower alkyl substituted amino;

X is = N- or = C(Z)-,

wherein Z is H, -R4, -C $\equiv$ C-CH<sub>2</sub>-R5, C(P) $\equiv$ C(Q)-R3,

wherein

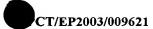
P and Q independently are H, lower alkyl or aryl,

R3 is aryl, aryl-lower alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl,

wherein R3 is independently, optionally substituted by one or more groups, e.g. 1-3 groups, selected from halo, hydroxy, oxo, lower alkoxy, CN or NO<sub>2</sub>, or optionally substituted (optionally mono- or di-lower alkyl substituted amino, aryl, aryl-lower alkyl, N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein the optional substitution comprises from 1 to 3 substituents selected from halo, hydroxy, lower alkoxy, CN, NO<sub>2</sub>, or optionally mono- or di-lower alkyl substituted amino)),

R4 is H, aryl, aryl-lower alkyl, aryl-lower-alkenyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl, and wherein

R5 is aryl, aryl-lower alkyl, aryloxy, aroyl or N-heterocyclyl as defined above, and wherein R5 is optionally substituted by R7 which represents from 1 to 5 substitutents selected from halo, hydroxy, CN, NO<sub>2</sub> or oxo, or optionally substituted (lower-alkoxy,



lower-alkyl, aryl, aryloxy, aroyl, lower-alkylsulphonyl, arylsulphonyl, optionally monoor di-lower alkyl substituted amino, or N-heterocyclyl, or N-heterocyclyl-lower alkyl,
wherein N-heterocyclyl denotes a saturated, partially unsaturated or aromatic nitrogen
containing heterocyclic moiety attached via a nitrogen atom thereof having from 3 to 8
ring atoms optionally containing a further 1, 2 or 3 heteroatoms selected from N, NR6, O,
S, S(O) or S(O)<sub>2</sub> wherein R6 is H or optionally substituted (lower alkyl, carboxy, acyl
(including both lower alkyl acyl, e.g. formyl, acetyl or propionyl, or aryl acyl, e.g.
benzoyl), amido, aryl, S(O) or S(O)<sub>2</sub>), and wherein the N-heterocyclyl is optionally fused
in a bicyclic structure, e.g. with a benzene or pyridine ring, and wherein the Nheterocyclyl is optionally linked in a spiro structure with a 3 to 8 membered cycloalkyl or
heterocyclic ring wherein the heterocyclic ring has from 3 to 10 ring members and
contains from 1 to 3 heteroatoms selected from N, NR6, O, S, S(O) or S(O)<sub>2</sub> wherein R6
is as defined above), and

wherein heterocyclyl denotes a ring having from 3 to 10 ring members and containing from 1 to 3 heteroatoms selected from N, NR6, O, S, S(O) or S(O)<sub>2</sub> wherein R6 is as defined above), and

and

wherein R7 is optionally substituted by from 1 to 3 substitutents selected from halo, hydroxy, optionally mono- or di- lower-alkyl substituted amino, lower-alkyl carbonyl, lower-alkoxy or lower-alkylamido;

Y is -NR8R9,

wherein

R8 is H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl), wherein R8 is optionally substituted by R10 which represents from 1 to 4 substitutents selected from halo, hydroxy, CN, NO<sub>2</sub>, -O-C(O)-, optionally substituted (lower-alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, lower-alkoxy, lower-alkenyl, lower-alkynyl, optionally mono- or di-lower alkyl-substituted amino or N-heterocyclyl (as defined above), wherein R10 is optionally substituted by R11 which represents from 1 to 4 substituents

selected from halo, hydroxy, CN, NO2, oxo, optionally substituted (optionally mono- or



di-lower alkyl-substituted amino, lower alkyl, optionally-lower alkyl substituted COOH, sulphinyl, sulphonyl, or N-heterocyclyl (as defined above))

wherein R11 is optionally substituted by R12 which represents from 1 to 4 substituents selected from halo, hydroxy, CN, NO<sub>2</sub>, oxo, hydroxy lower alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, optionally lower alkyl-substituted carboxy, hydroximine, or N-heterocyclyl as defined above, and

wherein

R9 is independently H, or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl), and

wherein R9 is optionally substituted by halo, hydroxy, oxo, lower alkoxy, CN, NO<sub>2</sub>, or optionally mono- or di-lower alkyl substituted amino;

or Z and Y together with the carbon atoms to which they are attached are joined to provide a compound of formula I selected from,

$$\begin{array}{c|c}
 & R \\
 & N \\
 & N \\
 & N \\
 & C \geq N
\end{array}$$
Ib

or

wherein

R is as defined above;



R15 is lower-alkyl,  $C_3$ - $C_{10}$ cycloalkyl,  $C_3$ - $C_{10}$ cycloalkyl-lower alkyl, NR20R21-lower alkyl-, where

T is -O- or a direct bond;

R16 is NR20R21-lower alkyl- or R4, both as defined above,

R20 is H, optionally substituted (lower alkyl, aryl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, lower alkoxy lower alkyl C<sub>3</sub>-C<sub>10</sub>cycloalkyl-lower alkyl or aryl lower alkyl),

R21 is optionally substituted (lower alkyl, aryl,  $C_3$ - $C_{10}$ cycloalkyl, lower alkoxy lower alkyl,  $C_3$ - $C_{10}$ cycloalkyl-lower alkyl or aryl-lower alkyl), or

R20 and R21 form an N-heterocyclyl ring as hereinbefore defined,

and wherein R20 or R21 are independently optionally substituted by R23 which which represents from 1 to 3 substitutents selected from halo, hydroxy, CN, NO<sub>2</sub>, oxo, optionally mono- or di-lower alkyl substituted amino, or optionally substituted (lower-alkoxy, lower-alkyl, lower alkoxy carbonyl, aryl-lower alkyl, aryl-lower alkenyl, aryloxy, aroyl, alkylsulphonyl, arylsulphonyl or N-heterocyclyl or N-heterocyclyl-lower alkyl (wherein N-heterocyclyl is as defined above));

A is -CH = or -C(O), B is -C = or -N, D is -CH = or -C(O) and E is -CH = or -N(R1) (where R1 is as defined above).

2. A compound according to claim 1 of formula lb, Ic, II, or IV or a pharmaceutically acceptable salt or ester thereof



R16 
$$N$$
 Ic

or

wherein

R8' is H or optionally substituted aryl-lower alkyl wherein R8' is optionally substituted as defined above for R8, and the other symbols are as defined above.

3. A compound according to claim 1 or a pharmaceutically acceptable salt or ester thereof selected from a compound of formula VI, VII, VIII or IX



wherein the symbols are as defined above.

- 4. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, selected from any one of the Examples 1, 11,12, 13, .
- 5. A compound according to claim 1 for use as a pharmaceutical.



- 6. A pharmaceutical composition comprising a compound according to claim 1 as an active ingredient.
- 7. A method of treating a patient suffering from or susceptible to a disease or medical condition in which cathepsin K is implicated, comprising administering an effective amount of a compound according to claim 1 to the patient.
- 8. The use of a compound according to claim 1 for the preparation of a medicament for therapeutic or prophylactic treatment of a disease or medical condition in which cathepsin K is implicated.
- 9. A process for the preparation of a compound of formula I or a salt or ester thereof which comprises
  - i) for the preparation of compounds of formula VI or pharmaceutically acceptable salts or esters thereof

wherein R2 and R15 are as defined above, cyanation of a corresponding 2-halo precursor of formula XIV

wherein R2 and R15 are as defined above and Halo is preferably Cl;



ii) for preparation of compounds of formula VII or pharmaceutically acceptable salts or esters thereof

wherein R2 and R16 are as defined above, coupling of a 6-hydroxy precursor of formula XV with an R16-Halo precursor

wherein R2 and R16 are as defined above and Halo is preferably Cl; iii) for the preparation of compounds of formula VIII or pharmaceutically acceptable salts or esters thereof

wherein R2 and R5 are as defined above, coupling of a 5-halopyrimidine precursor of formula XVI with a corresponding R5-CH₂-C≡CH propyne

wherein R2 and R5 are as defined above and Halo is preferably Br;



iv) for the preparation of compounds of formula IX or pharmaceutically acceptable salts or esters thereof

wherein R2 is as defined above and R8" is optionally substituted aryl-lower alkyl as defined above for R8', coupling of a secondary amine precursor of formula XVII

wherein R2 is as defined above, with a corresponding R8"-Halo precursor, wherein Halo is preferably I;

- v) thereafter, if desired, converting the product obtained into a further compound of formula I, or into a salt or ester thereof.
- 10 All novel products, processes and uses substantially as herein described with particular reference to the Examples.